Menopausal Hormones and Breast Cancer in a Biracial Population

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A B S T R A C T

Objectives. This study examined the association between menopausal hormones and breast cancer in a biracial population.

Methods. Logistic regression was used to calculate odds ratios for breast cancer associated with hormone use among 397 cases and 425 controls, all menopausal women.

Results. Odds ratios for ever use of hormones were 0.8 (95% confidence interval [CI] = 0.5, 1.2) for White women and 0.7 (95% CI = 0.4, 1.2) for Black women. Risk was not increased with longer duration of use or more recent use.

Conclusions. Breast cancer risk was not increased among White or Black women who used menopausal hormones, despite patterns of use varying considerably between races. (*Am J Public Health*. 2000;90:966–971)

The relationship between menopausal hormones and breast cancer has been investigated extensively, yet an increased risk has not been shown consistently.[1] Nonetheless, several meta-analyses and a collaborative reanalysis of 51 studies concluded that long-term hormone use increases risk by 20% to 35%, particularly among current users.[2–5]

Among the many studies of this association, none has focused on Black women. The risk associated with hormone use may differ between Black and White women.

Black women more frequently have estrogen receptor-negative breast cancers.[6] Genotype frequencies for certain estrogen-metabolizing enzymes vary between races,[7,8] although the significance of these observations is currently unknown. Finally, Black women have a high prevalence of obesity,[9] and body mass index (BMI) reportedly modifies the relationship between hormones and breast cancer, with stronger associations among leaner women.[5]

We examined the association between menopausal hormones and breast cancer in a case–control study in North Carolina. Approximately 40% of the study population were Black women, so we had an opportunity to compare patterns of hormone use and the association with breast cancer between racial groups.

Methods

The Carolina Breast Cancer Study was a population-based, case–control study.[10,11] Eligible cases were aged 20 to 74 years and were first given the diagnosis of invasive breast cancer between 1993 and 1996. Black women and women younger than 50 were oversampled with a modification of randomized recruitment.[12] Controls were selected from the *Division of Motor Vehicle* (ages 20–64) and Medicare (ages 65–74) lists. Sampling fractions based on race and 5-year age groups were implemented to ensure approximate frequency matching to cases. Women of all races were included, but White and Black women constituted the vast majority of the population. Other races, representing 1.6% of the study population, were included with White women for race-specific analyses.

Among women who were located and eligible, 77% of the cases and 68% of the controls were interviewed.[13] Case response rates ranged from 83% for White women younger than 50 years to 68% for Black women 50 years or older. Control response rates ranged from 73% for White women younger than 50 years to 59% for Black women 50 years or older.

Participants were interviewed in person to obtain data on established and suspected breast cancer risk factors. Questions on noncontraceptive hormones ascertained the type of hormone, dose, age at first and last use, duration of use, and treatment regimen. A pictorial display of commonly prescribed estrogens and progestins helped participants to recall hormonal information.

The analyses examined 397 cases and 425 controls who were menopausal. We included women who reported natural menopause, bilateral oophorectomy, or menopause caused by chemotherapy or radiation unrelated to breast cancer. Women who had a hysterectomy without bilateral oophorectomy were included if they were 50 years or older. We also included women who were presumably menopausal but could not specify a date for cessation of menses because they started hormones before their periods had stopped completely.

We used the SAS GENMOD procedure (SAS Institute Inc, Cary, NC) to calculate odds ratios (ORs) and 95% confidence intervals (CIs) with logistic regression models. Women who used oral or transdermal hormones for 3 months or longer were categorized as ever users. Covariates included in multivariate models were age (in 5-year increments), type of menopause (natural, bilateral oophorectomy, or other), age at menarche, number of full-term pregnancies, lactation history, history of breast cancer in

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This brief was accepted January 3, 2000.

a first-degree relative, BMI quartiles, education, alcohol consumption, and smoking. A term for race was included in models not stratified by race. Age at menopause was examined as an additional covariate, but women whose age at menopause was unknown were excluded from these models. Odds ratios from models including age at menopause were not substantially changed from those without it; thus, results are presented for the latter models.

Results

Characteristics of hormone users and nonusers among control women are shown in Table 1. The odds ratios show the association between each covariate and hormone use. Ever use of hormones was reported more commonly by White (65%) than by Black (39%) controls. Mean duration of use was 90 months for White women and 63 months for Black women. Among both races, hormone use was more common among women who had undergone bilateral oophorectomy, nulliparous women, women who had never lactated, and women who drank alcohol. Oral contraceptive use, higher education, and smoking were associated with hormone use only among Black women, whereas history of breast biopsy was associated with hormone use only among White women. The associations with family history and age at menarche were in opposite directions for

TABLE 1—Selected Characteristics of Hormone Users and Nonusers Among Controls, by Race: Carolina Breast Cancer Study

	White Women			Black Women		
	Users (n = 159)	Nonusers (n = 85)		Users (n = 71)	Nonusers (n = 110)	
	%	%	OR[a] (95% CI)	%	%	OR[a] (95% CI)
Age at selection, y						
≤40	1.3	1.2		1.4	0.9	
41–50	20.1	12.9		36.6	10.0	
51–60	35.2	20.0		26.8	34.6	
61–74	43.4	65.9		35.2	54.6	
Type of menopause						
Natural	32.7	69.4	1.0	12.7	65.5	1.0
Bilateral oophorectomy	30.2	5.9	9.5 (3.5, 26.0)	66.2	12.7	23.1 (9.2, 58.4)
Other[b]	37.1	24.7	3.1 (1.7, 5.9)	21.1	21.8	5.1 (1.9, 13.2)
No. of full-term pregnancies						
0	10.1	5.9	1.0	11.3	10.9	1.0
1	13.2	10.6	0.8 (0.2, 2.9)	14.1	14.6	0.7 (0.2, 2.4)
2	39.6	34.1	0.6 (0.2, 1.9)	18.3	15.5	0.8 (0.2, 2.7)
≥3	37.1	49.4	0.5 (0.2, 1.6)	56.3	59.1	0.8 (0.3, 2.2)
Breast-fed						
Never	64.8	51.8	1.0	62.0	45.5	1.0
Ever	35.2	48.2	0.6 (0.4, 1.1)	38.0	54.5	0.7 (0.4, 1.4)
Age at menarche, y						
≤11	15.8	18.8	1.0	26.8	16.5	1.0
12–13	62.0	56.5	1.4 (0.7, 2.9)	46.5	47.7	0.6 (0.3, 1.3)
≥14	22.2	24.7	1.4 (0.6, 3.2)	26.8	35.8	0.5 (0.2, 1.2)
History of breast cancer in first-degree relative						
No	88.0	80.5	1.0	84.3	87.2	1.0
Yes	12.0	19.5	0.6 (0.3, 1.3)	15.7	12.8	1.6 (0.6, 3.9)
History of breast biopsy						
No	71.7	80.0	1.0	82.9	86.2	1.0
Yes	28.3	20.0	1.7 (0.9, 3.3)	17.1	13.8	1.1 (0.5, 2.7)
Oral contraceptive use						
Never	49.4	54.1	1.0	46.5	74.5	1.0
Ever	50.6	45.9	0.8 (0.4, 1.5)	53.5	25.5	2.4 (1.2, 4.8)
Education, y						
<12	15.1	17.7	1.0	29.6	53.6	1.0
12	28.3	29.4	1.0 (0.4, 2.2)	38.0	15.5	3.4 (1.5, 7.7)
>12	56.6	52.9	1.1 (0.5, 2.3)	32.4	30.9	1.4 (0.6, 3.0)
BMI quartile, kg/m^2						
1st (<24.00)	36.1	31.8	1.0	11.4	11.9	1.0
2nd (24.00–27.69)	30.4	24.7	1.1 (0.5, 2.1)	22.9	18.4	1.0 (0.3, 3.2)
3rd (27.70–32.49)	20.3	32.9	0.5 (0.3, 1.1)	30.0	22.0	1.1 (0.4, 3.2)
4th (≥32.50)	13.3	10.6	1.0 (0.4, 2.5)	35.7	47.7	0.6 (0.2, 1.7)
Alcohol use						
Never	33.3	42.3	1.0	28.2	49.1	1.0
Ever	66.7	57.6	1.3 (0.7, 2.3)	71.8	50.9	2.0 (1.0, 3.9)
Smoker						
Never	50.3	41.2	1.0	47.9	70.0	1.0
Ever	49.7	58.8	0.7 (0.4, 1.2)	52.1	30.0	2.3 (1.2, 4.4)

Note. BMI = body mass index; OR = odds ratio; CI = confidence interval.
[a]Adjusted for age.
[b]Includes women who had a hysterectomy without bilateral oophorectomy, women who underwent menopause caused by chemotherapy or radiation unrelated to breast cancer, and women who began taking hormones before their periods had stopped completely.

Black and White women. BMI was not associated with hormone use in either race.

Table 2 presents characteristics of cases and controls stratified by race. Among both races, older age at menopause, natural menopause, earlier age at menarche, and never breast-feeding were more common among cases than controls. Nulliparity and family history of breast cancer were associated with breast cancer among White but not among Black women. Previous breast biopsy, oral contraceptive use, education, BMI, alcohol use, and smoking history were not associated with breast cancer in either race.

Odds ratios and 95% confidence intervals associated with hormone use for White and Black women are shown in Table 3. Ever use of hormones did not increase breast cancer risk for either White (OR=0.8, 95% CI=0.5, 1.2) or Black women (OR=0.7, 95% CI=0.4, 1.2). No consistent trends of increasing risk with longer duration of use or more recent use were found. Odds ratios were similar for women who used estrogen alone and those who used estrogen plus progestin. These analyses included both women who had always used progestin with estrogen and those who had used unopposed estrogen at some point. Odds ratios greater than 1 were observed for women who used progestin alone, although few women were in that category.

Among women reporting estrogen use, 73% used only conjugated estrogens, and an additional 14% used conjugated estrogens and other estrogens. Consequently, we had limited power to explore variations in risk by

TABLE 2—Selected Characteristics of Cases and Controls, by Race: Carolina Breast Cancer Study

	White Women			Black Women		
	Cases (n=222)	Controls (n=244)		Cases (n=175)	Controls (n=181)	
	%	%	OR[a] (95% CI)	%	%	OR[a] (95% CI)
Type of menopause						
Natural	60.4	45.5	1.0	54.3	44.8	1.0
Bilateral oophorectomy	16.7	21.7	0.5 (0.3, 0.9)	20.0	33.7	0.5 (0.3, 0.8)
Other	23.0	32.8	0.5 (0.3, 0.8)	25.7	21.6	1.0 (0.6, 1.7)
Age at menopause, y						
<45	35.6	43.8	1.0	47.7	50.0	1.0
45–54	58.8	50.0	1.6 (1.0, 2.3)	44.2	45.5	1.0 (0.7, 1.6)
≥55	5.6	6.2	1.2 (0.5, 2.8)	8.1	4.6	1.8 (0.7, 4.6)
Age at menarche, y						
≤11	19.8	16.9	1.0	27.0	20.6	1.0
12–13	58.6	60.1	0.8 (0.5, 1.3)	47.1	47.2	0.7 (0.4, 1.3)
≥14	21.6	23.1	0.8 (0.4, 1.4)	25.9	32.2	0.6 (0.3, 1.0)
No. of full-term pregnancies						
0	14.0	8.6	1.0	12.6	11.1	1.0
1	15.8	12.3	0.8 (0.4, 1.7)	13.1	14.4	0.8 (0.4, 1.9)
2	33.8	37.7	0.6 (0.3, 1.1)	18.3	16.6	1.0 (0.5, 2.3)
≥3	36.5	41.4	0.6 (0.3, 1.1)	56.0	58.0	0.9 (0.5, 1.7)
Breast-fed						
Never	67.6	60.2	1.0	57.1	51.9	1.0
Ever	32.4	39.8	0.7 (0.5, 1.0)	42.9	48.1	0.8 (0.5, 1.2)
History of breast cancer in first-degree relative						
No	80.8	85.3	1.0	90.0	86.1	1.0
Yes	19.2	14.7	1.4 (0.8, 2.3)	10.0	14.0	0.7 (0.4, 1.3)
History of breast biopsy						
No	74.8	74.6	1.0	84.4	84.9	1.0
Yes	25.2	25.4	1.0 (0.7, 1.6)	15.6	15.1	1.1 (0.6, 1.9)
Oral contraceptive use						
Never	51.8	51.0	1.0	65.1	63.5	1.0
Ever	48.2	49.0	1.0 (0.7, 1.6)	34.9	36.5	1.0 (0.6, 1.6)
Education, y						
<12	16.7	16.0	1.0	42.3	44.2	1.0
12	29.3	28.7	1.0 (0.6, 1.7)	26.3	24.3	1.2 (0.7, 2.1)
>12	54.1	55.3	0.9 (0.6, 1.6)	31.4	31.5	1.1 (0.7, 1.9)
BMI quartile, kg/m^2						
1st (<24.00)	37.3	34.6	1.0	15.5	11.7	1.0
2nd (24.00–27.69)	34.6	28.4	1.2 (0.8, 1.9)	18.5	20.1	0.7 (0.3, 1.5)
3rd (27.70–32.49)	16.6	24.7	0.6 (0.4, 1.1)	33.9	25.1	1.0 (0.5, 2.1)
4th (≥32.50)	11.5	12.4	0.8 (0.4, 1.6)	32.1	43.0	0.6 (0.3, 1.1)
Alcohol use						
Never	34.7	36.5	1.0	40.0	40.9	1.0
Ever	65.3	63.5	0.9 (0.6, 1.4)	60.0	59.1	0.9 (0.6, 1.4)
Smoker						
Never	45.1	47.1	1.0	55.4	61.3	1.0
Ever	55.0	52.9	0.9 (0.7, 1.4)	44.6	38.7	0.8 (0.5, 1.2)

Note. BMI=body mass index; OR=odds ratio; CI=confidence interval.
[a]Adjusted for age.

TABLE 3—Odd Ratios (ORs) for Breast Cancer Associated With Use of Menopausal Hormones, by Race: Carolina Breast Cancer Study

	All Women			White Women			Black Women		
	Cases (n = 384)	Controls (n = 420)		Cases (n = 217)	Controls (n = 242)		Cases (n = 167)	Controls (n = 178)	
	%	%	OR[a] (95% CI)	%	%	OR[b] (95% CI)	%	%	OR[b] (95% CI)
Never	56.3	45.9	1.0	45.2	35.1	1.0	70.7	60.7	1.0
Ever	43.8	54.1	0.8 (0.5, 1.1)	54.8	64.9	0.8 (0.5, 1.2)	29.3	39.3	0.7 (0.4, 1.2)
Duration of use, y									
<1	5.7	6.2	0.9 (0.4, 1.6)	6.5	5.4	1.0 (0.4, 2.4)	4.8	7.3	0.6 (0.2, 1.7)
≥1, <5	15.1	20.9	0.6 (0.4, 0.9)	18.0	24.0	0.6 (0.4, 1.0)	11.4	16.9	0.6 (0.3, 1.3)
≥5, <10	10.7	10.7	1.0 (0.6, 1.8)	12.4	13.6	1.0 (0.5, 1.8)	8.4	6.7	1.0 (0.4, 2.6)
≥10	12.2	16.2	0.8 (0.5, 1.2)	18.0	21.9	0.8 (0.4, 1.5)	4.8	8.4	0.6 (0.2, 1.5)
Time since last use, y									
<1	31.0	39.3	0.7 (0.5, 1.1)	41.5	50.8	0.7 (0.5, 1.2)	17.4	23.6	0.6 (0.3, 1.2)
≥1, <5	6.0	4.8	1.2 (0.6, 2.3)	6.5	4.6	1.4 (0.6, 3.4)	5.4	5.1	1.0 (0.3, 3.0)
≥5, <10	1.6	2.6	0.5 (0.2, 1.4)	0.9	2.9	0.2 (0.04, 1.0)	2.4	2.3	0.9 (0.2, 4.1)
≥10	5.2	7.4	0.7 (0.4, 1.4)	6.0	6.6	0.8 (0.3, 1.9)	4.2	8.4	0.6 (0.2, 1.7)
Type of hormone									
Estrogen only	24.5	33.8	0.8 (0.5, 1.2)	26.7	33.5	0.9 (0.5, 1.6)	21.6	34.3	0.6 (0.3, 1.1)
Progestin only	0.5	0.2	2.0 (0.2, 23.7)	0.9	0.4	1.8 (0.1, 23.2)	0.0	0.0	. . .
Estrogen and progestin	16.9	18.8	0.7 (0.4, 1.1)	24.4	28.9	0.6 (0.4, 1.0)	7.2	5.0	0.9 (0.3, 2.4)
Estrogen and progestin, never simultaneously	1.8	1.2	1.5 (0.4, 5.1)	2.8	2.1	1.2 (0.3, 4.6)	0.6	0.0	. . .
Type of estrogen									
Conjugated estrogens	31.9	39.4	0.8 (0.5, 1.1)	40.5	47.7	0.8 (0.5, 1.2)	21.0	28.1	0.7 (0.4, 1.3)
Other oral estrogen	2.6	3.6	0.6 (0.3, 1.5)	4.2	5.0	0.6 (0.2, 1.7)	0.6	1.7	0.4 (0.04, 4.8)
Transdermal estrogen	1.8	0.9	1.7 (0.5, 6.5)	1.9	0.8	2.5 (0.4, 15.3)	1.8	1.1	0.9 (0.1, 6.4)
Multiple estrogens	6.0	8.8	0.6 (0.3, 1.1)	6.5	9.5	0.7 (0.3, 1.6)	5.4	7.9	0.4 (0.1, 1.1)
Unknown type	1.1	1.2	0.7 (0.2, 2.9)	1.4	1.7	0.5 (0.1, 2.6)	0.6	0.6	1.4 (0.1, 27.1)
Conjugated estrogen dose, mg									
≤0.625	21.0	27.7	0.7 (0.5, 1.1)	26.5	34.5	0.7 (0.4, 1.1)	14.4	19.0	0.7 (0.4, 1.5)
>0.625	7.7	9.8	0.8 (0.4, 1.5)	8.7	11.0	0.7 (0.3, 1.5)	6.5	8.2	1.0 (0.3, 2.9)
Multiple doses	4.1	3.9	1.0 (0.4, 2.4)	7.0	7.0	0.9 (0.4, 2.3)	0.7	0.0	. . .
Unknown dose	3.3	4.7	0.7 (0.3, 1.6)	4.9	5.0	0.9 (0.3, 2.5)	1.3	4.4	0.3 (0.1, 1.8)

Note. CI = confidence interval.
[a]Adjusted for age, race, type of menopause (natural, bilateral oophorectomy, other), age at menarche, number of full-term pregnancies, lactation history, history of breast cancer in a first-degree relative, body mass index quartiles, education, alcohol consumption, and smoking.
[b]Covariates were the same as for all women, except the race term was excluded from the model.

type of estrogen. Increased risk was suggested among White women who used transdermal estrogen, but the analysis was based on very few women. Analyses restricted to conjugated estrogen users showed little evidence of a dose–response relationship.

Analyses stratified by BMI did not show greater risk for thinner women (BMI less than the race-specific median value among controls). Among Black women, odds ratios for breast cancer were 0.4 (95% CI = 0.2, 0.9) for thinner women and 1.8 (95% CI = 0.7, 4.3) for heavier women. Among White women, odds ratios were 0.9 (95% CI = 0.5, 1.6) and 0.7 (95% CI = 0.4, 1.3) for thinner and heavier women, respectively.

Discussion

Overall, we found essentially no evidence of increased breast cancer risk among menopausal hormone users in this biracial population. Odds ratios for ever use of hormones were less than 1 for both Black and White women; however, the confidence intervals around these point estimates were consistent with modestly increased risk. Similarly, there was little suggestion of increased risk within subgroup analyses examining duration or recency of use, type of estrogen, or dose of conjugated estrogens. The risks were similar for women who used estrogen alone and those who used estrogen plus progestin.

This report, to our knowledge, is the first to provide data on menopausal hormones and breast cancer among Black women. Race-specific analyses did not reveal important differences between Black and White women. A possible exception is the finding of increased risk among heavier Black women. This result, based on strata with relatively few women, was unexpected given the conclusions of the collaborative analysis[5] and should be interpreted cautiously.

A source of bias may have been response rate differences between cases and controls and the association between nonparticipation and hormone use. Women who declined an in-person interview were asked to complete a brief telephone survey on basic breast cancer risk factors. Both case and control women who responded to only the telephone survey reported hormone use less commonly than women who completed the in-person interview.[13] Assuming that hormone use was similarly low among women who completely refused to participate, the observed odds ratios were likely biased away from the null, resulting in stronger inverse relationships, because response rates were lower among controls than cases. This bias may have been most pronounced among Black women because response rates were lowest among older Black controls. However, it seems unlikely that this bias would have been large enough to obscure a significantly increased risk of breast cancer associated with hormones, especially because the prevalence of hormone use in our population was similar to that reported in 2 surveys of Black women.[14,15]

Our findings of no increased risk of breast cancer associated with menopausal hormone use are inconsistent with conclusions reached by the collaborative reanalysis and 2 major US cohort studies.[5,16,17] This outcome may be the result of having few long-term users in our population. However, several other studies that were larger than the Carolina Breast Cancer Study also found no increased risk of invasive breast cancer associated with hormone use.[18–20] It has been suggested that many biases inherent in observational studies, particularly those related to who receives hormone therapy, would tend to underestimate the risk of breast cancer associated with hormone replacement therapy.[21] Therefore, although our point estimates were generally less than 1, it is conceivable that a modest increase in risk was obscured by biases that could not be fully addressed within observational studies.

Although no important racial differences were seen in the association between hormone use and breast cancer, our descriptive analyses show striking differences between Black and White women in patterns of hormone use. Among controls, 65% of the White women but only 39% of the Black women had used menopausal hormones. Notably, nearly one quarter of Black women who had had a bilateral oophorectomy reported no hormone use. Similar racial differences in hormone use have been reported previously.[14]

The racial variation in hormone use may be attributable to both patient and physician factors. Although Black women report menopausal symptoms as frequently as White women do, they perceive the symptoms as less bothersome.[22,23] In addition, Black women may rely more on family members than medical professionals for some health care needs and information.[24] Therefore, they may request hormones for menopausal symptoms from physicians less often than do White women.

Menopausal symptoms, of course, represent only one indication for hormonal therapy. We had no data on the reasons that women took hormones; however, the lower prevalence and shorter duration of use among Black women suggest that hormones were prescribed less frequently for preventive reasons. In this population, Black women had lower socioeconomic status as measured by education or income than White women did. Some studies report that physicians are less likely to recommend preventive measures to poorer women because of cost concerns.[25] However, because menopausal hormones may be most beneficial among women at higher risk for cardiovascular disease[26] and Black women have a higher prevalence of cardiovascular risk factors,[9] greater use of hormones may be warranted.

In conclusion, breast cancer risk was not increased among Black or White women who used menopausal hormones. Although modestly increased breast cancer risk could have important public health implications because of the many women exposed, these results should be considered in terms of the overall risks and benefits. Many researchers have concluded that the benefits outweigh the risks for most women,[26–29] yet fear of cancer leads many women to discontinue or never begin hormone therapy.[30,31] Physicians must thoroughly explain expected benefits, risks, and side effects when prescribing hormones, allowing women to make informed decisions about hormonal therapy for menopausal symptoms and prevention of osteoporosis and cardiovascular disease. □

Contributors

P. G. Moorman, R. C. Millikan, and B. Newman designed and directed the Carolina Breast Cancer Study and developed the analysis strategies. H. Kuwabara performed the statistical analyses. P. G. Moorman supervised the data analysis and wrote the paper with input provided by each of the other authors.

Acknowledgments

This work was supported by a Specialized Program of Research Excellence (SPORE) in Breast Cancer grant (P50-CA58223) and a FIRST award (R29-CA67285) (P.G.M.), both funded by the National Cancer Institute.

The authors wish to thank the Carolina Breast Cancer Study nurse–interviewers: Carolyn Dunmore, Dianne Mattingly, Cheryl Robinson, Theresa Nalevaiko, and Patricia Plummer.

The study protocol of the Carolina Breast Cancer Study was approved by the human subjects committee of the University of North Carolina School of Medicine and the participating hospitals. Signed informed consent was given by all interviewed women.

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